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DNA Adducts using Accelerator Mass Spectrometry

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DNA adducts are DNA bases covalently modified by reactive chemical intermediates. The DNA adduct is believed to be mechanistically involved in carcinogenesis, and has been extensively researched for use as a biomarker for carcinogen exposure. DNA adducts have also been used as an endpoint in studies of biochemical mechanisms and to help understand the relationship between high dose animal exposures and low dose human exposures. Numerous methods have been applied to the measurement of DNA adducts in animal studies and in some human exposure situations, but most have had difficulty quantifying adducts at real human exposure levels. Questions remain on the nature of dose-response relationships, how adducts in animal models reflect humans, and whether adduct levels can be used to reflect carcinogen exposure at low doses.

Accelerator mass spectrometry (AMS) is a high sensitivity method for measuring isotope ratios that has been applied to the measurement of DNA adducts. AMS measures radiocarbon-labeled chemicals with attomole sensitivity. DNA adducts have been measured by AMS to levels of a few adducts/10^{12} nucleotides, corresponding to less than 1 DNA adduct/cell. AMS has been applied to the study of dose-response relationships for carcinogens and to studies in humans. The results of these studies are showing that DNA adduct formation is generally linear with dose in rodents given the carcinogens trichloroethylene, benzene, MeIQx, and PhIP, although some saturation may occur at high doses (mgs/kg). No threshold has been observed at low dose for any of these agents. Direct comparison of adduct formation in humans and animals given well-defined doses of the dietary heterocyclic amine MeIQx has shown that colon adduct levels is up to 10-times greater in humans than rodents, although the same adduct types are present. Finally, metabolite and individual adduct tracing by AMS is being developed to allow detailed biochemical mechanisms to be explored and related at low dose.

This approach of using AMS to measure adducts following low dose exposures in humans and animals, as well as in dosimetry studies, should help in the risk assessment process, in determining the value of DNA adducts for use as biomarkers for carcinogen exposure and in studies using adducts as endpoints in humans. This work performed under the auspices of the U.S. DOE by LLNL (W-7405-ENG-48) and partially supported by the NIH (ES04705, CA55861), US Army (MM4559FLB) and the Health Effects Institute (#94-5).